AMENDMENTS TO THE SPECIFICATION

Please amend the specification as detailed below. As required under 37 C.F.R. § 1.121(b)(1), marked-up versions of the paragraphs to be replaced are below.

Please amend paragraph [0001] of the application as follows:

[0001] This application is a continuation-in-part of U.S. Patent Application Serial No. 10/763,498, ~~entitled "NOVEL ANTI-ARRHYTHMIC AND HEART FAILURE DRUGS THAT TARGET THE LEAK IN THE RYANODINE RECEPTOR (RYR2)", and~~ filed on January 22, 2004, now abandoned, ~~which is a continuation-in-part of U.S. Patent Application Serial No. 10/680,988, filed on October 7, 2003, which is a continuation-in-part of U.S. Patent Application Serial No. 10/608,723, filed on June 26, 2003, which is a continuation-in-part of U.S. Patent Application Serial No. 10/288,606, filed on November 5, 2002, which is a continuation of U.S. Patent Application Serial No. 09/568,474, filed on May 10, 2000, now U.S. Patent 6,489,125 B1, issued on December 3, 2002,~~ the contents of which ~~are~~ is hereby incorporated by reference herein.

Please amend paragraph [0153] of the specification as filed, which corresponds to paragraph [0244] of the published application, as follows:

[0244] The inventors' compounds have significantly reduced blocking of hERG (I(Kr)) channels, when compared with JTV-519. As shown in FIGS. 15-18, [[4-7,]] for example, one of the inventors' compounds, S36, has hERG blocking activity that is approximately 5- to 10-fold lower than the hERG blocking activity of JTV-519. Because the inventors' compounds have weak hERG blocking activity, they are expected to be less toxic than JTV-519.

Please <u>insert</u> the below paragraphs after paragraph [0033] of the specification as filed, which corresponds to paragraph [0062] of the published application, and renumber the following paragraphs as necessary:

[0034] FIG. 15 demonstrates the experimental protocol used to test effects of the inventors' novel JTV-519-related compounds (disclosed herein) on hERG-channel current. Whole-cell patch-clamp experiments were carried out with physiological solutions at room temperature, in CHO cells transfected with hERG channel. Voltage-clamp protocols are shown in the lower panels. In vehicle, 0.1% DMSO in the external solution was applied with the same time-protocol as that shown in the upper panel.

[0035] FIG. 16 illustrates the effects of JTV-519 and the inventors' novel JTV-519-related compound, S36 (disclosed herein), on hERG-channel currents elicited by 80-mV depolarization. Representative hERG-channel currents (I(Kr)) were recorded from CHO cells before (open circle) and after (closed circle) application of 1 μM JTV-519 (left panel) or 1 μM JTV-S36 (right panel). The voltage-clamp protocol is shown below the current traces. Currents were elicited during 400-msec depolarization to +80 mV, from a holding potential of -90 mV. It should be noted that, upon the 400-msec depolarization (which mimics the human action potential duration (APD)), hERG channels pass very little outward current, because they rapidly inactivate. Tail currents marked by circles in current traces were elicited by return of the membrane potential to -40 mV, in the recovery from inactivation through the open state. Because the tail current is a major contributor to control of the APD, effects of the drugs were evaluated by tail currents at -40 mV: JTV-519 = 83% block; JTV-S36 = 39% block.

[0036] FIG. 17 shows effects of JTV-519, E4031, and the inventors' novel JTV-519-related compound, S36 (disclosed herein), on activation of hERG-channel currents (traces). Representative hERG-channel I-V relationships are shown before (control, left panels) and after (central panels) application of 0.1% DMSO (vehicle; upper central panel), 1 μM JTV-519 (middle central panel), and 1 μM JTV-S36 (lower central panel). The right panel shows that 5 μM E4031 (a class III anti-arrhythmic drug known to block hERG channels) completely blocked hERG-channel currents. (Note the tail currents at -40 mV). The voltage-clamp protocol is set forth in FIG. 15, as an I-V relationship.

[0037] FIG. 18 demonstrates effects of JTV-519 and the inventors' novel JTV-519-related compound, S36 (disclosed herein), on activation of hERG-channel currents. The hERG-channel I-V relationships are shown for peak tail currents (activation) before (open squares) and after (closed squares) application of 0.1% DMSO (vehicle; upper panel), 1 μM 15 JTV-519 (lower left panel), and 1 μM JTV-S36 (lower right panel). Washout of the drugs is depicted with open triangles. The voltage-clamp protocol is set forth in FIG. 4, as an I-V relationship. It should be noted that JTV-S36 did not block hERG currents at negative potentials (0 mV; 20 mV depolarization) showing voltage-dependent block of I(Kr).